

# Post-Myocardial Infarction Depression

## Summary

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### Introduction

Major depression is common among patients recovering from a myocardial infarction (MI).<sup>1-5</sup> Additionally, clinically significant depressive symptoms are present in other patients whose symptom severity or duration does not meet established criteria for a diagnosis of major depression.<sup>5</sup> Over the last decade, increasing evidence suggests that in addition to its effect on quality of life, post-MI depression also deserves attention because of a reported relation to increased morbidity and mortality.<sup>5-8</sup>

This evidence report reviews the studies that have examined depression or depressive symptoms in patients after an MI and focuses on the prevalence, clinical significance, treatment, and methods of evaluating this condition. A number of studies have evaluated various aspects of post-MI depression including prevalence,<sup>1-4,9-27</sup> its association with mortality,<sup>5-10,20,28-36</sup> and major adverse events,<sup>25,26,31,37-39</sup> and treatment.<sup>10,40-47</sup> This report addresses the following key questions regarding post-MI depression.

1. In patients diagnosed with and hospitalized for acute MI, what is the prevalence of depression during initial hospitalization for MI? Depression was defined as symptoms of depression meeting established threshold criteria by psychiatric interview or validated questionnaire.
- 1a. What is the prevalence of depression during initial hospitalization for an acute MI, with and without a history of previous depression as reported by study investigators?
2. What percentage of patients with post-MI depression continue to have depression (or depressive symptoms) one or more months after initial hospital discharge?
3. What is the association of post-MI depression with outcomes independent of other predictors of post-MI outcomes? Post-MI outcomes include:
  - Clinical outcomes—total mortality, cardiac mortality, MI, resuscitated arrest, stroke, arrhythmias, and revascularization.
  - Quality of life.
  - Utilization of health care services—readmission, total hospital days, and cost of care. Potential predictors include demographic and clinical characteristics of patients that have been reported to be associated with the risk of post-MI outcomes.
- 3a. What is the association of post-MI depression with surrogate markers of cardiac risk independent of other predictors of post-MI outcomes? Surrogate markers of disease severity include: heart rate variability, platelet reactivity, and markers of inflammation such as C-reactive protein.



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4. Do post-MI patients with depression have better outcomes with depression treatment compared to those without depression treatment? Depression treatment includes all interventions intended to have specific impact on depression, such as antidepressants, cognitive behavioral therapy, inter-personal therapy, psychosocial support, and cardiac rehabilitation.
  - 4a. Do outcomes differ with or without improvement in depression for post-MI patients with depression that do receive depression treatment?
  - 4b. Do outcomes differ with or without improvement in depression for post-MI patients with depression that do not receive depression treatment?
5. What are the performance characteristics (e.g., sensitivity, specificity, reliability, and predictive value) of instruments or methods that are used to screen for depression (or depressive symptoms) following an acute MI?
  - 5a. What are the performance characteristics of instruments or methods that are used to screen for depression (or depressive symptoms) following an acute MI, during hospitalization?
  - 5b. What are the performance characteristics of instruments or methods that are used to screen for depression (or depressive symptoms) following an acute MI, within three months after hospitalization?
6. Does the use of cardiac treatment for patients with acute MI differ for those with and without depression? Cardiac treatment includes: revascularization (angioplasty or bypass surgery), angiotensin converting enzyme (ACE) inhibitors, beta blockers, statins, antiplatelet agents, or other treatments recommended by the American Heart Association or the American College of Cardiology.

## Methods

The Johns Hopkins University Evidence-based Practice Center (EPC) assembled a team including clinicians and researchers from diverse specialties including cardiology, psychiatry, general internal medicine, and cardiac rehabilitation. The EPC team then recruited eight technical experts to provide input regarding the choice of key questions. The expert review panel consisted of a representative from the EPC's partner organization, the American Academy of Family Physicians, as well as investigators active in post-MI depression research including those from cardiology, psychiatry and psychology, nursing, cardiac rehabilitation, and representatives of private and governmental payers.

## Literature Search

The EPC team performed a comprehensive search that included electronic and hand searching. In March 2004, we searched the following electronic databases: MEDLINE<sup>®</sup>, the Cochrane CENTRAL<sup>®</sup> Register of Controlled Trials (Issue 1, 2003), the Cochrane Database of Methodology Reviews (CDMR<sup>®</sup>), the Cumulative Index of Nursing and Allied Health Literature (CINAHL<sup>®</sup>), the Psychological Abstracts (PsycINFO<sup>®</sup>), and EMBASE<sup>®</sup>.

Hand searching for possibly relevant articles was performed by three techniques. First, the EPC team identified 16 journals that we thought were most likely to contain relevant studies and scanned the table of contents of each of these journals for relevant citations from October 2003 to April 2004. Second, we reviewed references cited in recent review articles for inclusion. Third we examined the reference lists of eligible articles for additional articles that might be relevant.

Two members of the EPC team independently reviewed the abstracts identified by the search to exclude those that did not meet the eligibility criteria. Primary studies were eligible if they addressed one of the key questions, included original human data, were not case reports, and were written in the English language. Individual key questions had additional exclusion criteria. When two reviewers agreed that an abstract was not eligible, it was excluded from further review.

To focus the evidence report on the studies that would be most valuable in addressing the key questions, we used the following additional eligibility criteria:

- For key question 4 we excluded studies that did not include a concurrent comparison group.
- For key question 5, we excluded studies that did not use a validated reference standard.

## Review Process

Paired reviewers assessed the quality of each eligible article. Differences between the paired reviewers were resolved by face-to-face discussion. The reviewers assigned points for the quality of the studies based on information about the representativeness of the patients included in the study, the potential for bias and confounding, the description of the intervention or evaluation, the adequacy of followup, and the appropriateness of the statistical methods. The score for each category of study quality was the percentage of the total points available in each category for that study, and could range from zero to 100 percent.

One reviewer in each pair was the primary reviewer who abstracted data from the article. The second reviewer confirmed the accuracy of the first reviewer's work.

## Results

### Key Question 1

In patients diagnosed with and hospitalized for acute MI what is the prevalence of depression during initial hospitalization for MI?

- Twenty-five articles met criteria for inclusion in this review.<sup>1-5,9-27,48</sup>
- Articles were published between 1986 and 2004.
- Eight studies used a structured clinical interview,<sup>1-3,5,10,16,17,49</sup> and 17 used a validated questionnaire.<sup>4,5,9,11-15,18-25,50</sup>
- Major depression was reported in about one of every five patients hospitalized for an MI. The reported prevalence of potentially significant symptoms of depression varied widely (range 10 to 47 percent).
- In general, the reported prevalence of potentially significant symptoms of depression was higher when it was based on a Beck Depression Inventory (BDI)<sup>5, 9,18-23,50</sup> than when based on a Hospital Anxiety and Depression Scale (HADS)<sup>12-15</sup>; this may be because the BDI includes somatic symptoms that may overlap with MI symptoms, whereas the HADS does not.

**Key Question 1a.** What is the prevalence of depression during initial hospitalization for an acute MI, with and without a history of previous depression as reported by study investigators?

There was insufficient data to address this question.

### Key Question 2

What percentage of patients with post-MI depression continues to have depression (or depressive symptoms) one or more months after initial hospital discharge?

- We found 22 articles that met criteria for inclusion in this review.<sup>2,12,14,18-20,22,23,25,26,38,51-61</sup>
- Nine of the 22 used a standardized clinical interview to diagnose depression.<sup>10,26,51-57</sup>
- Only three studies reported the prevalence of depression in patients during the MI hospitalization and then specifically re-assessed and reported the prevalence in these same patients at followup.<sup>2,18,23</sup>

- Based on these three studies, most patients with depression during the initial MI hospitalization continue to have depression 1 to 4 months later.

### Key Question 3

What is the association of post-MI depression with outcomes independent of other predictors of post-MI outcomes?

- Sixteen studies addressed the relationship of post-MI depression and mortality.<sup>5-10,20,28-36</sup>
- Mortality has been assessed as early as 4 months<sup>5</sup> and as late as 10 years after MI.<sup>7</sup>
- The evidence indicates that post-MI depression is associated with a significantly increased risk of death.
- A single study indicated that post-MI depression is associated with increased cardiac re-admission in the first year after MI.<sup>39</sup>
- Six studies reported on cardiac events in relationship to post-MI depression.<sup>25,26,31,37-39</sup> The three studies reporting a positive relationship between post-MI depression and cardiac events<sup>31,37,39</sup> were generally larger than the three studies finding no relationship<sup>25,26,38</sup> suggesting that the latter may have had insufficient power to detect differences if they, in fact, were present.
- Depression during the initial hospitalization was related to poor quality of life in the first year after MI.<sup>13,30,59,62</sup>

**Key Question 3a.** What is the association of post-MI depression with surrogate markers of cardiac risk independent of other predictors of post-MI outcomes?

- Three studies examined the association of post-MI depression with heart rate variability, platelet activity, and inflammatory markers (one study for each surrogate marker).<sup>57,63,64</sup>
- All three studies reported surrogate markers of increased risk in patients with post-MI depression, even after adjustment for covariates.

### Key Question 4

Do post-MI patients with depression have better outcomes with depression treatment compared to those without depression treatment?

- Twelve studies, 11 of which were randomized controlled trials, addressed this question.<sup>10,40-47,65-67</sup> The studies were published between 1991 and 2003.
- In post-MI patients with depression, psychosocial intervention improves depression but not other outcomes.<sup>10,44</sup>

- In post-MI patients with depression, selective serotonin reuptake inhibitors improve depression and some surrogate markers of cardiac risk, but no studies of sufficient power address the question of whether this treatment improves survival.<sup>45,46,65,66</sup>

**Key Question 4a.** Do outcomes differ with or without improvement in depression for post-MI patients with depression that do receive depression treatment?

There was insufficient data to address this question.

**Key question 4b.** Do outcomes differ with or without improvement in depression for post-MI patients with depression that do not receive depression treatment?

There was insufficient data to address this question.

## Key Question 5

What are the performance characteristics (e.g., sensitivity, specificity, reliability, and predictive value) of instruments or methods that are used to screen for depression (or depressive symptoms) following an acute MI?

- We found six studies published between 1968 and 1988 meeting criteria to address this issue.<sup>14,18,56,68-70</sup>
- Of the six studies, four were from Europe,<sup>14,56,68,70</sup> one from Canada<sup>18</sup> and one from the United States.<sup>69</sup>
- All included studies reported exclusively on post-MI populations.
- None of the instruments reported had been normalized specifically for post-MI patients.
- The BDI tended to be more sensitive to lower levels of depressive symptoms but less sensitive to more severe depression compared to the HADS and the Symptom Checklist-90 Depression scale.

**Key question 5a.** What are the performance characteristics of instruments or methods that are used to screen for depression (or depressive symptoms) following an acute MI during hospitalization?

There was insufficient data to address this question.

**Key question 5b.** What are the performance characteristics of instruments or methods that are used to screen for depression (or depressive symptoms) following an acute MI, within three months after hospitalization?

There was insufficient data to address this question.

## Key Question 6

Does the use of cardiac treatment for patients with acute MI differ for those with and without depression?

- Nine studies published between 1982 and 2004 met criteria for review on this question.<sup>23,26,37,50,71-75</sup>
- Four studies compared prescribed discharge medications and were inconsistent in their findings: United States and United Kingdom<sup>50,71</sup> studies suggested decreased prescriptions of beta-blockers and aspirin, while European<sup>26</sup> and Canadian<sup>23</sup> studies found no difference.
- Three studies compared adherence to prescribed medications and lifestyle modifications and consistently found decreased adherence among depressed patients.<sup>71-73</sup>
- Two studies compared use of cardiac procedures and reached divergent conclusions about the use of procedures in post-MI patients.<sup>23,37</sup>
- Two studies assessed completion of cardiac rehabilitation but had insufficient numbers to reach conclusions about the influence of depression on completion of rehabilitation.<sup>74,76</sup>

## Discussion

### Key Question 1

Major depression is reported in about one of every five patients hospitalized for MI. This proportion is fairly consistent among the eight studies that used a structured clinical interview to establish this diagnosis. The reported prevalence of potentially significant symptoms of depression varies more widely (range 10 to 47 percent). This wide range of reported prevalence rates appears to be due almost exclusively to differences in measurement instruments used, and even to differences in threshold criteria applied from study to study when the same instrument was used. In general, the reported prevalence of potentially significant symptoms of depression is higher when this diagnosis is based on a BDI score of 10 or higher than when it is based on a HADS score of either 8 or higher or 11 or higher. This difference may be attributed to the BDI's inclusion of somatic symptoms that may overlap with MI symptoms, whereas the HADS does not include somatic symptoms and is designed for use in hospitalized patients.

Additional studies also are needed to define the most clinically-relevant measure of depression during the initial MI hospitalization. Studies are needed to determine the clinical or demographic factors that are associated with post-MI depression.

### Key Question 2

Although 22 studies reported the prevalence of depression in patients 1 month or longer after initial hospital discharge, only

three reported the prevalence of depression in patients during the MI hospitalization and then specifically reassessed and reported the prevalence of depression in these same patients at followup. These studies suggest that most patients (60 to 70 percent) with depression during the initial MI hospitalization continue to have depression (or depressive symptoms) 1 to 4 months later.

Additional studies are needed that assess depression (or depressive symptoms) in groups of patients during the initial hospitalization and at various time points after MI. Studies of patients who are reassessed for depression at multiple time points post-MI are also needed.

### **Key Question 3**

Sixteen studies evaluated the relationship between depression, measured shortly after an acute MI, and subsequent mortality. Studies have assessed this relationship as early as 4 months post-MI and as late as 10 years post-MI. Despite the facts that various measures of depression have been used, that different subgroups of depressed patients have been evaluated, and that different post-MI survival times have been assessed, the weight of the evidence is strikingly consistent. Overall, the evidence supports the notion that post-MI depression is associated with a significantly increased risk for subsequent death, whether by cardiac or other causes. Depression appears to be associated with about a 3-fold increased risk of cardiac mortality per se based on at least three studies that addressed cardiac mortality in a total of almost 2,000 patients.<sup>39,77,78</sup> Depression during the initial hospitalization is associated with poor quality of life in the first year after an MI.

During the first year after MI, depression during the initial MI hospitalization has been found to be inversely related to physical quality of life, social quality of life of women, sexual activity and satisfaction among men, return to work of employed men, and to physical, psychological, and social health and function. Limitations of the above mentioned studies included the variety of diagnostic instruments used to assess depression; the lack of agreement on what aspects of quality of life are of greatest import or how to measure included studies; the degree to which potential confounders were adequately considered; and the absence of data in early post-MI time points.

Additional studies are needed to determine the major cause(s) of mortality among depressed post-MI patients. Additional studies also are needed to determine whether patients with depression are at higher risk for malignant arrhythmias than comparable post-MI patients without depression.

**Key question 3a.** A small amount of evidence suggests that post-MI patients with depression have alterations in autonomic function as reflected by decreased heart rate variability, increased platelet activity, and increased levels of soluble adhesion molecule 4. These studies suggest that the risk associated with post-MI depression could be transmitted by multiple biological pathways.

Additional studies are needed to elucidate the mechanism(s) responsible for increased mortality in patients with post-MI depression. Particular emphasis should be placed on surrogate markers which have been previously associated with increased risk without regard to depression, including markers for sudden death including heart rate variability, T-wave alternans, etc, and inflammatory markers including C-reactive protein, interleukins, adhesion molecules and others. Studies are needed that evaluate the hemostatic and platelet function of patients with post-MI depression. Future studies also should address whether responses to commonly used antiplatelet agents differ among post-MI patients with versus without depression.

### **Key Question 4**

No studies of sufficient power have yet been performed that directly address the question as to whether treatment with antidepressants improves survival in depressed patients after an MI. Some evidence suggests that selective serotonin reuptake inhibitor antidepressants have beneficial effects on surrogate markers of post-MI risk (e.g., heart rate variability, aortic time velocity integral). There is evidence that both psychosocial intervention and selective serotonin reuptake inhibitor antidepressants improve depression in post-MI patients. However, the possibility of increases in rare adverse events cannot be excluded.

Studies are needed to determine whether patients with depression who are treated for depression, especially with highly effective drugs, differ in outcomes from patients who are not treated. Future studies should also determine whether treatment for depression per se or resolution of depression is associated with different outcomes.

### **Key Question 5**

There are insufficient data to allow an adequate assessment of the performance characteristics of instruments or methods used to screen for depression during the initial MI hospitalization. The very low positive predictive values of these screening instruments (generally in the 25 to 50 percent range) may be acceptable clinically if followed by a more thorough assessment of those who screen positive; however, the low positive predictive values are particularly problematic if used to detect relationships to outcome variables in the research setting. When compared with the HADS and Symptom Checklist-90

Depression scale, the BDI tends to diagnose less significant symptoms of depression at higher rates. It may be less effective in accurately diagnosing major depression.

Additional studies are needed to determine the performance characteristics of instruments or methods used to screen for depression (or depressive symptoms) during the initial MI hospitalization. Studies are needed in post-MI patients that examine the ability for depression screening instruments or methods to distinguish symptoms of depression from symptoms attributable to the MI, to poor physical health, or to the hospitalization itself.

## Key Question 6

It remains unclear whether there are significant differences in cardiac medications prescribed to post-MI patients based on the presence or absence of depression. Three studies evaluated adherence to prescribed medications and secondary prevention measures in post-MI patients and consistently found lower adherence in those with depression than those without depression. Two good-quality studies, using different methods, came to diverse conclusions about whether the frequency with which cardiac procedures are used varies between post-MI patients with depression and those without depression.

Additional large studies are needed to examine whether the use of diagnostic and therapeutic procedures differs between depressed and non-depressed post-MI patients. Future studies should also address whether potential differences in procedures are due to differences in provider recommendation or to differences in patient acceptance. Further studies are needed to determine whether the treatment prescribed to post-MI patients with depression differs from those without depression. Future studies should address whether the non-pharmacologic interventions (including diet, exercise and cardiac rehabilitation) recommended to post-MI patients differ between those patients with and without post-MI depression. Future studies should examine the adherence behavior of post-MI patients and evaluate measures that could improve adherence to recommended treatment.

## Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by The Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018. It is expected to be available in spring 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology

Assessment No. 123, *Post-Myocardial Infarction Depression*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at [www.ahrq.gov](http://www.ahrq.gov).

## Suggested Citation

Bush DE, Ziegelstein RC, Patel UV, Thombs BD, Ford DE, Fauerbach JA, McCann UD, Stewart KJ, Tsilidis KK, Patel AL, Feuerstein CJ, Bass EB. Post-Myocardial Infarction Depression. Summary, Evidence Report/Technology Assessment No. 123. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.) AHRQ Publication No. 05-E018-1. Rockville, MD: Agency for Healthcare Research and Quality. May 2005.

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